METHOD OF TREATING OCULAR DISEASES BY PERIOCULAR ADMINISTRATION OF CYCLOSPORINE A OR G

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to a method for treating ocular disease and, more specifically, to a method for treating ocular disease by administration of cyclosporine A or G to a patient through a periocular injection pharmaceutically acceptable carrier to a patient.

2. Description of Related Art

Cyclosporines A and G belong to a class of structurally distinct, cyclic, poly-N-methylated undecapeptides having valuable pharmacological, in particular immunosuppressive, anti-inflammatory and anti-protozoal activity. The first to be isolated and the "parent" compound of this class is the naturally occurring fungal metabolite "cyclosporine," also known as cyclosporine A, the production and properties of which are described for example in U.S. Pat. No. 4,117,118. Note that use of the term "cyclosporin(e)" alone is generally recognized in the art to refer only to cyclosporine A unless otherwise stated. Since the original discovery of cyclosporine A, a wide variety of a naturally occurring cyclosporines have been isolated and identified and many further non-natural cyclosporines have been prepared by synthetic or semisynthetic means or by the application of modified cultured techniques. The class comprised by the cyclosporines is thus now substantial and includes, for example, the naturally occurring cyclosporines A, C, D and G, as well as various semisynthetic derivatives thereof, such as their dihydroderivatives, as disclosed, e.g., in U.S. Pat. Nos. 4,108,985; 4,210,581 and 4,220,641, and other natural and artificial cyclosporines such as those disclosed in European Patent Publication No. 0058,134 B1.

Cyclosporine A has been used in the treatment of ocular disease mediated by immune processes. Lately, cyclosporine A has been used locally in the form of ophthalmic drops for the treatment of disorders involving the anterior portion of the eye and conjunctiva with good results as reported at Holland et al, ("Immunohistologic Findings and Results of Treatment With Cyclosporine in Ligneous Conjunctivitis," *Amer. J. of Ophthalmology,* 107:160–166, Feb. 1989). Cyclosporin A has also been used in an ophthalmic treatment by topical administration thereof to the eye (U.S. Pat. No. 4,649,047 to Kaswan), as well as for increasing tear production by topical administration thereof (U.S. Pat. No. 4,839,342 to Kaswan).

A concern with cyclosporine A has been its potential to cause nephrotoxicity. Systemic therapy with cyclosporine A has been associated with renal toxicity (kidney failure) and increased incidence of opportunistic infections. The systemic side effects of cyclosporine A are so severe that they sometimes limit its use to life-threatening or severe sight-threatening diseases. Topical application of this drug can lead to systemic absorption with measurable plasma levels if given often enough for severe local inflammatory conditions, such as corneal graft rejection. In individuals such as newborns, those with renal disease, or those taking non-steroidal anti-inflammatory agents, this has the increased potential to limit the usefulness of cyclosporine A.

As an alternative agent for treating ocular diseases, cyclosporine G has been evaluated in an ocular inflammatory model and it is found to be at least 80% as effective as cyclosporine A at equivalent intracameral dosages as reported by Nussenblatt et al ("A Comparison of the Effectiveness of Cyclosporine A, D and G in the Treatment of Experimental Autoimmune Uveitis in Rats," *J. of Immunopharmacology,* 8(3), (1986), pp. 427–435). Cyclosporin G differs from cyclosporine A in that the L-nor-valine has replaced alpha-amino butyric acid at the amino acid 2 position. Cyclosporine G has a molecular weight of 1217, as compared to cyclosporine A with a molecular weight of 1203. Cyclosporine G has also been found not to be as nephrotoxic as cyclosporine A as reported by Calne et al ("Cyclosporin G: Immunosuppressive Effect in Dogs with Renal Allografts," Lancet ii:1342, 1985). However, previous reported results have indicated that topical administration of cyclosporine G does not prevent the expression of experimental autoimmune uveitis, Nussenblatt et al ((1986 , pp. 427–435).

Accordingly, there exists a strong need for developing a local ocular therapeutic route which eliminates the undesirable physiological problems associated with the cyclosporine A treatment of ocular diseases, while maintaining the advantageous therapeutic properties of this treatment.

Applicants have now surprisingly discovered that administration of cyclosporine A or G by periocular injection may be used to treat ocular diseases including serious intraocular inflammatory processes requiring immunosuppression for a sustained period; and further that periocular administration of cyclosporine G to a patient may be used to effectively treat ocular diseases including endogenous uveitis, Behcet's Disease, corneal transplantation, vernal keratoconjunctivitis, ligneous keratoconjunctivitis, dry eye syndrome, anterior uveitis and onchocerciasis.

SUMMARY OF THE INVENTION

Accordingly, it is an object of this invention to provide a method for the treatment of various ocular diseases.

It is another object of the present invention to provide a method for effectively treating ocular diseases while lowering the risks of undesirable physiological problems, such as nephrotoxicity, associated with conventional treatments, such as those using cyclosporine A.

It is still another object of the present invention to provide a method for the treatment of ocular diseases by administration of cyclosporine A or G through periocular injection into the patient.

It is a further object of the present invention to provide an effective method for the treatment of ocular diseases including endogenous uveitis, Behcet's Disease, corneal transplantation, vernal keratoconjunctivitis, ligneous keratoconjunctivitis, dry eye syndrome, anterior uveitis and onchocerciasis.

Applicants have discovered that these objects of the present invention are surprising satisfied by administration of cyclosporine A or G through periocular injection thereof in a pharmaceutically acceptable carrier in order to effectively treat ocular diseases with advantageously reduced concern of the undesirable physiological effects associated with previous treatments.